

Proposed Decision Memo for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N)

Decision Summary

On December 20, 2006, we initiated the national coverage determination process by opening a tracking sheet for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N). After examining the available medical evidence, we propose that no national coverage determination is appropriate at this time, and that the §1862(a)(1)(A) decision should be made by local contractors through a local coverage determination process or case-by-case adjudication. See *Heckler v. Ringer*, 466 U.S. 602, 617 (1984) (Recognizing that the Secretary has discretion to either establish a generally applicable rule or to allow individual adjudication.) See also, 68 Fed. Reg. 63692, 63693 (November 7, 2003).

Our examination of the published medical evidence does not provide sufficient information that would enable CMS to define specific populations of patients who would benefit from a particular treatment with particular medications at this time. Because a national coverage determination is defined, in part, as including “whether or not a particular item or service is covered nationally” under title XVIII, §§ 1862(l), 1869(f)(1)(B), we do not believe a national policy is possible or prudent at this time. Still, in order to maintain an open and transparent process, we are seeking comments on our proposal that no national coverage determination is appropriate at this time. We will respond to public comments in a final decision memorandum, consistent with the spirit of §1862(l)(3).

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Proposed Decision Memo

TO: Administrative File: CAG #000345N
Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases

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SUBJECT: Proposed Decision Memorandum for Nebulized Beta Adrenergic Agonist Therapy for Lung Disease

DATE: June 20, 2007

I. Proposed Decision

On December 20, 2006, we initiated the national coverage determination(NCD) process by opening a tracking sheet for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N). After examining the available medical evidence, we propose that no national coverage determination is appropriate at this time, and that the §1862(a)(1)(A) decision should be made by local contractors through a local coverage determination process or case-by-case adjudication. See Heckler v. Ringer, 466 U.S. 602, 617 (1984) (Recognizing that the Secretary has discretion to either establish a generally applicable rule or to allow individual adjudication.) See also, 68 Fed. Reg. 63692, 63693 (November 7, 2003).

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II. Background

As way of background, we will further define certain terms that will be referenced throughout this document, including: beta adrenergic agonist drugs, bronchodilation, and lung diseases such as asthma and Chronic Obstructive Pulmonary Disease (COPD). Beta adrenergic agonist drugs are a class of medications used to treat lung diseases marked by partially or completely reversible bronchospasm. Alternative terms for beta adrenergic agonist drugs include beta agonists and β agonists, which may be considered to be interchangeable terms here. Bronchospasm refers to contraction of the smooth muscles of the bronchial wall, which leads to narrowing of the airway. This document also references the terms bronchodilation and bronchodilatation, which are interchangeable here. Bronchodilation and bronchodilatation are defined as an increase in the size of the lumen of the bronchus or bronchial tubes. When citing the writing of others we retain the original term. Lung function may be assessed in many ways. A common method is spirometry, where the volume and speed of a patient's airflow is measured and compared to expected results. Forced expiratory volume in one second (FEV1), peak expiratory flow rate (PEV or PEFr) and forced vital capacity (FVC) are measurements that are often obtained to assess the patient's baseline function and response to treatment. The abbreviation b.i.d. means two times per day and the abbreviation q.d. means once per day.

We also provide a brief summary of beta adrenergic agonist drugs and of the options for their administration to assist in the reader's understanding of this memorandum. As there are relatively few drugs in this class, it is clearer to illustrate intraclass similarities and differences by referring to specific drugs, especially when dealing with enantiomers (see below). Some of the drugs usually are self administered by the patient and, therefore, do not fall within a Medicare Part B benefit. § 1862(s)(2)(A). We consider them in this review because a summary of the treatment of lung disease would be inadequate otherwise.

Beta adrenergic agonist drugs may be classified as selective or nonselective, depending on their relative action on the beta-1 or beta-2 adrenergic receptor. Beta-1 receptors predominate in the heart, whereas beta-2 receptors predominate in the lungs. Thus, selectivity for the beta-2 receptor is a desired characteristic to minimize cardiac effects. Nonselective agents act on both receptors. Beta adrenergic agonist drugs may be classified as short or long acting, based on the duration of action. In patients with asthma, the use of long acting beta adrenergic(LABA) agonist drugs may increase the risk of asthma-related death

(<http://www.fda.gov/Cder/drug/infopage/LABA/default.htm>).

There are also differences between the US and other countries in the generic drug nomenclature and commercial availability of specific beta adrenergic agonist drugs. In this document we use the US nomenclature except when citing the writings of others. For the convenience of the reader, the beta adrenergic agonist drug known as albuterol in the US is known as salbutamol in other countries.

Though drugs in the same class often share chemical characteristics, we do note that certain pairs of beta adrenergic agonist drugs, levalbuterol and racemic albuterol, arformoterol and racemic formoterol; have a special relationship. Some drugs commonly exist as a racemic (50:50) mixture of the left and right enantiomers. Enantiomers are a type of isomer, i.e. chemicals with the same formula and similar structure, analogous to right and left hands. Levalbuterol and arformoterol are single enantiomers of albuterol and formoterol respectively. Essentially, racemic albuterol is half comprised of levalbuterol, and racemic formoterol is half comprised of arformoterol.

Combination pharmacotherapy is a widely used strategy to address treatment goals. Short or long acting beta adrenergic agonists are combined with anticholinergic or corticosteroid medications in order to maximize therapy.

Though there are a number of lung diseases that may cause bronchospasm, asthma and COPD are the two that are most prevalent and are the main indications for the use of these drugs. In addition, they are associated with considerable morbidity and mortality. A large body of clinical evidence has been developed that addresses several aspects of these diseases, including: disease natural history, pharmacologic and non-pharmacologic treatment options, disease exacerbation and progression. We provide a brief summary of these two conditions here.

COPD is a chronic lung disorder characterized by airflow limitation that is only partially reversible and generally progressive in nature. Approximately four to six percent of adults in the United States have been diagnosed with COPD, and COPD ranks as the fourth leading cause of death. The primary cause of COPD is exposure to tobacco smoke. Tobacco smoke accounts for 80-90% of the risk of developing COPD. In general, patients with COPD have smoked at least 20 cigarettes per day for a minimum of twenty years. They present in their early fifties, complaining of difficulty breathing or other acute illnesses of the chest. Symptoms can also include the production of sputum, chronic coughing, and occasionally wheezing. Persons who have a deficiency of the enzyme alpha-1-antitrypsin also have an increased risk of developing COPD.

Pharmacologic treatment of COPD is used to prevent and/or control daily symptoms, which are a major cause of disability for persons with this disease. Medications also help to decrease the frequency and severity of exacerbations. To date, pharmacologic treatments have not been shown to modify the long term disease progression, i.e. the decline in lung function that is the hallmark of this disease. Despite the limited reversibility of their airflow restriction, patients with COPD often report symptomatic improvement with the use of bronchodilator medications which are the hallmark of pharmacologic treatment. Common bronchodilator medications include beta adrenergic agonists, anticholinergics, and methylxanthines.

Asthma is a chronic inflammatory disorder of the airways associated with the clinical symptoms of wheezing, cough, chest tightness, and shortness of breath. The disease is marked by airway hyperreactivity and widespread reversible airflow obstruction. The etiology of asthma has not been fully defined. Current theories include exposure to allergens and the subsequent development of an inflammatory response in the airways. Asthma affects approximately five percent of the U.S. population. It is also responsible for over two million emergency department visits, some 470,000 hospitalizations, and 4,500 deaths annually.

Pharmacologic treatments in asthma are generally divided into two groups. The first group, bronchodilators, has previously been noted. The second group, anti-inflammatory drugs, acts to modify airway inflammation. The mainstay of therapy is the use of medications to decrease the airway inflammatory process and control airway hyperreactivity, i.e., heightened airway sensitivity to factors causing spasm or narrowing.

The goals of therapy for patients with bronchospastic lung diseases marked by complete or partial reversibility such as asthma or COPD, include- prevention of disease progression; relief of symptoms; improvement of health status; prevention and/or treatment of disease related complications; and prevention or minimalization of treatment related adverse events.

There are several available methods for delivering bronchodilator medications, depending on the medication chosen, including aerosolized inhalation and oral administration. The most widely used delivery method is aerosolized inhalation, which has been well established since the latter half of the twentieth century. Types of inhalation devices include nebulizers that require minimal patient cooperation and coordination, metered dose inhalers (MDI) that require the greatest amount of coordination, and dry powdered inhalers (DPI) which provide medication only when triggered by patient inhalation. An MDI is a pressurized pocket sized device that delivers medication directly into the lungs by using a propellant spray. The use of holding chambers (spacers) with the MDI helps to improve medication delivery by decreasing the effort required to coordinate inhalation with actuation. A DPI is a device that delivers medication as a fine powder directly into the lungs. Inhalation maximizes drug delivery directly into the lungs to achieve maximal drug concentrations within the lung parenchyma, decreases the time to onset of action, and reduces systemic effects. The effectiveness of inhalation is dependent on coordinated technique. Improper technique can result in decreased drug delivery and decreased medication efficacy.

A nebulizer is an electrical device approximately the size of a coffeemaker, and the patient or caregiver will bring the device into proximity of the patient and plug it into an electrical outlet. Typically, the administration of a drug via nebulizer involves several steps. Several feet of flexible tubing are attached at one end to the nebulizer. On the other (patient) end a small reservoir for the drug and diluent liquid is attached to the tubing. The reservoir is attached to a mouthpiece which is inserted into the patient's mouth. Prior to each use, the patient or caregiver will place the liquid medication in the reservoir. After the nebulizer is turned on the patient inhales through the mouthpiece for the 10-15 minutes needed to consume the drug.

III. History of Medicare Coverage

Currently, CMS does not have a NCD on the use of nebulized beta adrenergic agonist therapy for lung disease.

Current Request

On December 20, 2006, CMS internally generated and opened a national coverage analysis (NCA) for the use of nebulized beta adrenergic agonist therapy for the treatment of lung disease. We specifically focused on those lung diseases marked by bronchospasm that is at least partially reversible. Asthma and COPD are two prevalent examples of chronic lung diseases meeting these criteria.

Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one or more of the statutorily defined benefit categories outlined in the Social Security Act(the Act). § 1812 (scope of Part A); § 1832 (scope of Part B); § 1861(s) definition of medical and other services).

When a nebulizer is used to administer a beta adrenergic agonist medication, the equipment and the drug would be eligible for coverage under § 1861(s)(6) of the Act, durable medical equipment (DME). Medicare Benefits Policy Manual, § 110.3. DME is described in the regulations as equipment furnished by a supplier or a home health agency that: (1) can withstand repeated use; (2) is primarily and customarily used to serve a medical purpose; (3) generally is not useful to an individual in the absence of a illness or injury; and (4) is appropriate for use in the home. 42 C.F.R. § 414.202. The equipment and the drug are eligible for coverage under the DME benefit because the use of the equipment could not be deemed reasonable and necessary without the use of the appropriate drug.

Other Information

The DME benefit category is not applicable when a beta adrenergic agonist medication is administered via any type of disposable inhaler or other disposable items that do not meet the statutory definition of DME. Also, there is no benefit category for coverage under Medicare Part B of a beta adrenergic agonist medication when taken orally, as the medication is usually self-administered by the patient.

We note for the reader that oral, MDI and DPI preparations of beta adrenergic agonist drugs, which are not the subject of this analysis, may be covered by Medicare Part D plans.

IV. Timeline of Recent Activities

December CMS posted a tracking sheet on the website and the initial 30 day public comment period began. Due to technical difficulties with the website submission of comments, CMS accepted public comments through January 24, 2007.

May 31, 2007 Posted public comments.

V. The Food and Drug Administration(FDA) Status

FDA has approved a number of beta adrenergic agonists for a variety of uses. The table below summarizes those that are marketed for the treatment of one or more lung diseases.

Drug	Duration	Selectivity
Racemic albuterol	Short acting	Beta-2
Levalbuterol	Short acting	Beta-2
Racemic formoterol*	Long acting	Beta-2
Arformoterol	Long acting	Beta-2
Metaproterenol	Short acting	Less Beta-2 selective
Pirbuterol*	Short acting	Beta-2
Salmeterol*	Long acting	Beta-2

Drug	Duration	Selectivity
Terbutaline*	Short acting	Less Beta-2 selective

* not approved in the US in a nebulized formulation

This table reflects current information on the commercial availability of these drugs in the United States. In some cases these beta adrenergic agonist drugs may also be marketed in fixed dose combinations with another drug such as an anticholinergic. One such combination, albuterol and ipratropium (sometimes spelled ipratroprium, we use the former for consistency in this document) is commercially available as a nebulized treatment option for COPD patients requiring more than one bronchodilator for disease management.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination.

VII. Evidence

A. Introduction

We are providing a summary of the evidence that we considered during our review. The current stated evidence is not sufficient to identify a population for whom a particular covered medication should be covered nationally under Part A or Part B of Title XVIII of the Social Security Act. We will, of course, consider additional evidence submitted through the public comment period.

B. Discussion of evidence reviewed

1. Questions

1.

Is the evidence sufficient to conclude that nebulized beta agonist therapy improves health outcomes when used in the home by Medicare beneficiaries who have lung disease?

2.

If the answer to Question 1 is affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predict a favorable health outcome?

Outcomes

While measuring lung function in terms of FEV1, FVC, or PEFr performance can provide valuable information regarding the extent and prognosis of a patient's disease, it may not accurately reflect the level of day-to-day disease related disability. In addition, relatively modest changes in measured lung function tests may be associated with clinically significant improvements in health status and patient well-being. In general, there is a lack of validated, objective measures to appropriately evaluate and quantify common disease symptoms for patients with bronchospastic lung diseases that are at least partially reversible such as asthma and/or COPD. Studies evaluating treatment options for these diseases often provide results and information based on lung function but fail to address patient centered outcomes such as improvement in dyspnea, increased ability to participate in activities of daily living, or other quality of life measures.

2. External technology assessments

We did not request an external technology assessment on this issue and are unaware of any assessments that have been conducted independently.

3. Internal technology assessments

Literature Search

CMS performed an extensive literature search utilizing PubMed for randomized controlled trials (RCTs) and systematic reviews evaluating the use of nebulized beta adrenergic agonist therapy as part of a treatment regimen for lung diseases. The literature search was limited to the English language and specific to the human population.

Evidence Reviewed

Use in COPD

Sestini et al. (2002) performed a systematic review of thirteen studies assessing the clinical effectiveness and adverse effects of regular treatment with short-acting beta-2 agonist bronchodilators (albuterol, fenoterol, terbutaline, bitolterol, pirbuterol, reproterol, and metaproterenol) in adult patients with stable COPD. All studies reviewed were comparative RCTs of at least one week duration. The authors noted modest but statistically significant post-bronchodilator improvement in FEV1 and FVC when compared to placebo. Five trials reported data regarding treatment failure based on the number of patients who dropped out of the study due to disease exacerbation. Risk of treatment failure was greater in the placebo group (RR=0.49). In addition, post-bronchodilator peak flow measurements were higher in the treatment group. Improvements were also noted in daily breathlessness scores, dyspnea and fatigue with treatment when compared to placebo. No studies reported serious adverse events associated with treatment.

Datta et al. (2003) performed a randomized, double-blind, placebo-controlled, crossover trial comparing the bronchodilator effect (e.g. FEV1 at 0.5 hr and other time points following nebulization) and side effects (e.g. hand tremor) of single doses of nebulized levalbuterol with two commonly used as-needed bronchodilator regimens for COPD (racemic albuterol alone and combined with the anticholinergic drug ipratropium). One half hour following administration, all three nebulized bronchodilator treatments yielded improvements in FEV1 when compared to placebo. There were no statistically significant differences between groups during any time period. The effects of bronchodilator therapy on pulse rate, oxygen saturation, and tremor score were also measured. Albuterol and levalbuterol resulted in small increases in pulse rate at 0.5 hours. This increase disappeared by 1 hour. No significant differences were noted in oxygen saturation or tremor scores.

Appleton et al. (2006) performed a systematic review to determine the effectiveness of long acting β_2 agonists (LABAs) in COPD patients whose symptoms demonstrated poor reversibility with short acting bronchodilators. Twenty three RCTs comparing the regular use of salmeterol or formoterol to placebo over a four week period were evaluated. Outcome measures included: lung function tests, exercise tolerance, dyspnea symptoms, health related quality of life measures, exacerbations, and rescue medication usage. Authors noted statistically significant improvements in FEV1 and peak flow measurements when comparing salmeterol to placebo. Patients in the salmeterol 50mcg group also experienced reduced disease exacerbations and rescue inhalation use. The strength of the evidence for the use of salmeterol 100mcg, formoterol 12, 18, or 24mcg was insufficient to provide clear indications for clinical practice. Authors also noted inconsistent results when considering exercise tolerance, quality of life measures, and symptom scores.

Appleton et al. (2006) also performed a systematic review comparing the efficacy and safety of regular long term use of ipratropium bromide alone or in combination with LABAs (salmeterol or formoterol) compared to the use of LABAs alone. Seven RCTs of at least four weeks duration using inhaled or nebulized medications were included. Studies evaluating ipratropium versus LABAs showed statistically significant improvements in FEV1 and peak flow measurements for the salmeterol group. No significant differences in quality of life measures, dyspnea scores, symptom scores, exercise capacity, rescue inhalation use, number of exacerbations, and/or adverse events were noted. When comparing combination therapy with ipratropium and LABAs versus LABAs alone, statistically significant improvements in FEV1, FVC, quality of life measures, and decreased rescue bronchodilator use were noted with combination therapy. The study authors note formoterol offered a small benefit over ipratropium bromide when comparing morning peak flow measurements, an intermediate outcome. No differences were noted in disease exacerbations or significant adverse events.

The COMBIVENT Inhalation Solution Study Group (1997) performed a randomized safety and efficacy trial comparing the combination of ipratropium-albuterol with one or the other combination component separately. Six hundred fifty-two patients participated in the trial. Primary outcome measures included acute bronchodilator response as measured by FEV1, peak expiratory flow rate, quality of life measures, and adverse events. On each of the 4 test days, authors noted the mean peak response for the combination therapy was significantly greater than for either of its components. The combination mean change in FEV1 at peak ranged from 17-28% greater than ipratropium alone and 17-26% greater than albuterol alone. No statistically significant differences were noted in morning peak expiratory flow rates, quality of life measures, or the number of patients increasing their medication dosage or using additional medications. Greater than 50% of patients in each study group experienced at least one adverse event. Worsening of lower respiratory tract symptoms was the most commonly reported event.

Gross et al. (1998) performed a randomized, double blind cross-over trial to compare the effectiveness of nebulized albuterol-ipratropium versus each component medication. The primary efficacy outcome included percent change in FEV1 within 8 hours after dosing. Authors note mean percent change of the combination when compared to albuterol of 23.6% and ipratropium of 37.2% during the crossover phase of the trial. These results were statistically significant ($p < 0.001$). Results of the parallel phase of the trial were similar to those described above. No differences were noted with regard to the development of treatment related adverse events when comparing groups.

Tashkin et al. (1996) performed a randomized, double blind trial to compare the safety and efficacy of nebulized ipratropium with placebo versus nebulized ipratropium and metaproterenol. Patients received treatment three times per day for 85 days. Patients presented to the facility for evaluation on days 1, 43, and 85. Primary outcome measures included: subjective symptom control, pulmonary function measurements, and additional medication usage. On each test day, the treatment group showed a significant peak change and AUC (area under the curve) measurement for FEV1 ($p \leq 0.0002$). No significant changes in symptoms were noted when comparing the control and treatment groups. No significant differences were noted with regard to adverse events. The most common events included tremor and nervousness in the combination group and nausea in the control group.

Baumgartner et al. (2007) performed a 12-week, multicenter, randomized, double-blind, double-dummy, placebo - and active controlled trial of nebulized arformoterol (currently marketed as Brovana®) in patients with COPD. They compared three strengths of arformoterol, salmeterol by MDI, and placebo. The primary end point was mean change (%) from baseline in the morning trough FEV1 AUC. Of the 917 subjects enrolled, 724 were randomized and 717 actually received study medication. All active treatments were statistically significantly better than placebo in the primary outcome: arformoterol 15µg b.i.d. (+16.9%), 25µg b.i.d. (+18.9%), 50µg q.d. (+14.9%) and salmeterol 42 µg b.i.d. (+17.4%) and placebo (+6.0%). The authors concluded that arformoterol is an effective option for patients who could benefit from sustained bronchodilator therapy.

Use in Asthma

Nelson et al. (1998) evaluated the effects of levalbuterol in chronic asthmatic patients. The comparator arms included levalbuterol 0.63mg and 1.25mg, albuterol 1.25mg and 2.5mg, and placebo. The combined levalbuterol treatment groups had a statistically significant improvement in forced expiratory volume in one second (FEV1) when compared to the racemic albuterol group after the first dose of treatment but this effect was not seen by week four of treatment. Patients in all treatment arms used less rescue medication. Six percent of patients experienced adverse events leading to study withdrawal. The events most commonly reported by patients were asthma symptoms and were similar across treatment arms.

Pleskow et al. (2004) compared the effect of nebulized levalbuterol, albuterol, and placebo for regular three times a day use in chronic asthma. The study reported on changes in peak FEV1 and similar surrogate outcomes for all groups on the first day and at four weeks and found a statistically significant improvement in these intermediate outcomes for levalbuterol over albuterol for the first dose but no difference between the two active groups at 4 weeks.

Thompson, Wise, Rodenberg (2003) performed an open label controlled study in another acute setting, i.e. pre-hospital, ambulance-based emergency medical services. Overall peak flow rates improved from baseline in patients administered albuterol or levalbuterol. When comparing the agents no statistically significant differences were appreciated.

Nowak et al. (2006) conducted a multicenter, randomized, double-blind trial which compared nebulized levalbuterol and racemic albuterol in the treatment of adults with acute asthma exacerbations. The primary endpoint was time to meet ED discharge criteria. Secondary endpoints included changes in lung function and hospitalization rates. The trial identified small and statistically nonsignificant differences in treatment time to discharge and hospitalization rates favoring levalbuterol. The benefit of levalbuterol was most clearly observed in patients who at ED presentation were not on concomitant (inhaled or oral) corticosteroids and in those who had high plasma (S) albuterol concentrations.

Schreck and Babin (2005) conducted a retrospective review of emergency department patients presenting with acute asthma at 2 different sites over 9- and 3-month consecutive periods. Patients received either racemic albuterol or levalbuterol delivered via nebulizer in addition to other standard treatments including corticosteroids and oxygen. Outcome measures included ED hospital admission rate, length of stay, arrival acuity, and treatment costs. Significantly fewer admissions were observed in the levalbuterol vs racemic albuterol group in the first patient cohort (4.7% vs. 15.1%, $p=0.0016$). Similar results were noted in the second patient cohort (13.8% vs. 28.9%, $p=0.021$). The authors concluded that levalbuterol, when used in place of racemic albuterol, is cost-effective and reduces the number of hospital admissions in the treatment of acute asthma in the ED setting.

Rabe et al. (2006) performed a prospective 12 month, double-blind, parallel group study evaluating the effect of combination maintenance therapy with budesonide/formoterol and one of three as-needed medications (terbutaline, formoterol, or budesonide/formoterol). Primary outcome measures included time to first severe exacerbation (exacerbation requiring hospitalization, ED treatment, and or need for oral steroids for 3 days or more. The time to first severe exacerbation was prolonged with the combination of maintenance budesonide/formoterol along with as needed budesonide/formoterol or terbutaline. Rates of exacerbation requiring ED treatment or hospitalization were reduced with as needed budesonide/formoterol versus formoterol (27%, $p=0.46$) and by 39% ($p=0.0010$) versus terbutaline. Use of reliever medication decreased over time in all groups. High usage of short-acting beta adrenergic agonist has been associated with an increased risk of life-threatening asthma. The authors performed a post-hoc analysis of the patient population defined as requiring frequent use of reliever therapy. They noted patterns of high use were uncommon in all groups. Four deaths occurred during the study; none were determined to be causally related to the study drugs or reported as deaths caused by asthma.

4. MEDCAC

CMS did not convene the Medicare Evidence Development and Coverage Advisory Committee for this analysis.

5. Evidence-based guidelines

Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute. Global strategy for asthma management and prevention. Bethesda, MD 2005.

- Therapy should be selected on the basis of a patient's asthma, availability of anti-asthma medications, conditions of the health care system, and individual patient circumstances.
- For intermittent asthma, no daily medication is recommended. A rapid-acting inhaled beta₂-agonist may be taken as needed to relieve asthma symptoms.
- Patients with mild persistent asthma require controller medication every day. Treatment with an inhaled glucocorticosteroid is preferred.
- The preferred therapy for moderate persistent asthma is regular treatment with a combination of inhaled glucocorticosteroid and a long-acting inhaled beta₂-agonist twice daily.
- The primary therapy for severe persistent asthma includes inhaled glucocorticosteroid at higher doses plus a long-acting inhaled beta₂-agonist twice daily.
- Once control of asthma is achieved for at least 3 months, a gradual reduction of maintenance therapy should be tried.

Institute for Clinical Systems Improvement (ICSI). Diagnosis and outpatient management of asthma. March 2005.

- Mild Intermittent Asthma- no daily medications needed
- Mild Persistent- low dose inhaled corticosteroids preferred
- Moderate Persistent- low/medium dose inhaled corticosteroids plus long-acting beta₂-agonist preferred
- Severe Persistent- medium/high dose inhaled corticosteroid plus long-acting beta₂-agonist and/or leukotriene modifier, and/or theophylline
- Quick relief- short acting bronchodilator: inhaled beta₂-agonist as needed for symptoms with MDI spacer/holding chamber

Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. 2005

- Mild Intermittent Asthma- inhaled short acting beta₂ agonist as short term reliever therapy for all symptomatic patients.
- Step 2: Introduction of Regular Preventer Therapy
Inhaled steroids are recommended for preventer therapy for achieving overall treatment goals. Inhaled steroids should be considered for patients with any of the following: asthma exacerbations in the last two years, use of inhaled beta₂-agonists three times a week or more; symptomatic three times a week or more, or waking one night a week. Give inhaled steroid initially twice daily, may consider once daily if good control is established.

- **Step 3: Add-on Therapy**
Carry out a trial of other treatments before increasing the inhaled steroid dose above 800 micrograms/day in adults. The first choice for an add-on therapy to inhaled steroids is an inhaled long acting beta₂-agonist.
- **Step 4: Poor Control**
If control remains inadequate consider increasing inhaled steroids, leukotriene receptor antagonists, theophyllines, slow release beta₂-agonist tablets.

Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung, and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda, MD 2005.

- The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease.
- Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms.
- The principal bronchodilator treatments are β₂-agonists, anticholinergics, theophylline, and a combination of on or more of these drugs.
- Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.

Device Selection and Outcomes of Aerosol Therapy: Evidence-based Guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Dolovich MB, Aherns RC, Hess DR, et al. Chest 2005; 127: 335-371.

- For treatment of asthma in the outpatient setting, the MDI, with or without spacer/holding chamber, and the DPI are all appropriate for the delivery of short-acting β₂-agonists.
- The appropriate selection of a particular aerosol delivery device in this setting includes the patient's ability to use the device correctly, patient preference, availability of the drug/device combination, compatibility between the drug and device delivery, lack of time or skills to properly instruct the patient, cost of therapy, and potential for reimbursement.
- For treatment of COPD in the outpatient setting, the MDI, with or without spacer/holding chamber, the nebulizer, and the DPI are all appropriate for the delivery of inhaled β₂-agonist and anticholinergic agents.
- For outpatient COPD therapy, the selection of an appropriate aerosol delivery device for inhaled β₂-agonist and anticholinergic agents includes the patient's ability to use the device correctly, patient preference, availability of the drug/device combination, compatibility between the drug and device delivery, lack of time or skills to properly instruct the patient, cost of therapy, and potential for reimbursement.

Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group. The pharmacologic management of chronic obstructive pulmonary disease. Washington (DC): Veterans Health Administration, Department of Veterans Affairs; 2002 September.

- Because of a lower incidence of systemic adverse effects, inhaled bronchodilators are preferred to oral bronchodilators. The amount of inhaled medication deposited in the lung is in direct relation to the technique; therefore, providing education on the proper technique in the use of MDI is necessary. Spacers should be encouraged to enhance drug delivery. Consider other drug delivery systems if patient cannot use an MDI with spacer.

- There is little evidence that nebulizer delivery offers improvement in the management of stable COPD over that of an MDI with spacer. Patients who may benefit from drug delivery via nebulizer are those who have difficulty in using an MDI with spacer. Examples of patients who may be unable to use an MDI or dry-powder inhaler: those with impaired hand strength or dexterity, visual impairment, mental/cognitive problems, or inability to use an MDI during acute exacerbation. Nebulizer delivery should be continued only if there is a clear benefit.
- Short acting β_2 -agonists should be used as needed for the majority of patients with COPD.
- Symptoms may improve without substantial improvement in FEV₁ indicating that continuation of therapy does not depend on routine assessment of spirometry. Patients should be treated regardless of whether or not there is improvement in FEV₁ following bronchodilator administration.

Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004 Feb; 59 Suppl 1:1-232.

- Short-acting bronchodilators, as necessary, should be the initial treatment for relief of breathlessness and exercise limitation.
- Patients who remain symptomatic should have their treatment intensified to include long-acting bronchodilators or combined therapy.

Finnish Medical Society Duodecim. Chronic obstructive pulmonary disease (COPD). In: EBM Guidelines. Evidence-Based Medicine. Helsinki, Finland; 2005 March.

- Inhaled short acting or long acting anticholinergic drug first line treatment.
- Inhaled beta-sympathomimetic (salbutamol, terbutaline, fenoterol) may be combined with anticholinergic drug.

6. Professional Society Position Statements

American Thoracic Society, European Respiratory Society. Standards for the diagnosis and treatment of patients with chronic obstructive pulmonary disease. 2004

- The medications for COPD currently available can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status.
- At present no treatment is shown to modify the rate of decline in lung function.
- The change in lung function after brief treatment with any drug does not help in predicting other clinically related outcomes.
- The inhaled route is preferred.
- Combining different agents produces a greater change in spirometry and symptoms than single agents alone.

American Thoracic Society: Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med vol 152: pp S77-S120, 1995.

- Beta-agonists produce less bronchodilatation in COPD than in asthma; in some patients, spirometric changes may be insignificant despite symptomatic benefit. There is no evidence that early, regular use of pharmacotherapy can alter the progress of COPD. Thus, in patients with intermittent symptoms it is reasonable to initiate metered-dose inhaler therapy of a beta-selective bronchodilator only when needed for the relief of symptoms.
- Albuterol, pirbuterol, metaproterenol, terbutaline, or isoetharine is preferable to less selective drugs. A spacer should be used, if indicated, to improve aerosol delivery and reduce side effects.

7. Expert Opinion

CMS did not solicit or receive any expert opinion on this issue.

8. Public Comments

Initial public comments

Initial Comment Period 12/20/2006-01/19/2007

Due to feedback from commenters who experienced technical difficulties with the electronic submission of comments to the CMS website this comment period was extended to 1/24/2007. As noted above CMS uses the initial public comments to inform its proposed decision. CMS responses to comments about the drugs themselves are, as customary, incorporated into our analysis. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

CMS received a total of 82 comments during the first public comment period. Fifty-six (67 %) of the 82 comments are against restricting the Medicare Part B coverage of levalbuterol. The distribution of these commenters is as follows: 16 clinicians, two health care non clinicians, one patient, 36 organizations and one unidentified. Eight (10%) of the commenters (three clinicians, one health care non clinician, and five organizations) favored some type of coverage guidelines for the use of levalbuterol in the treatment for patients with asthma and COPD. Eighteen (23 %) of the comments (one clinician, one patient, six health care non clinicians, and eight organizations) pertained to issues outside of the purview of this national coverage analyses, e.g. least costly alternative (LCA), FDA drug approval process, and compounding of drugs.

CMS received very few comments directly or indirectly from patients utilizing nebulized beta adrenergic therapy. One was from a patient who is being treated with nebulized beta adrenergic agonist therapy; one commenter expressed an interest in the findings of this analysis; and one comment was from a family member of a patient who is being treated with nebulized beta adrenergic agonist therapy.

Several of the commenters commented on the scope of the NCA and suggested that CMS withdraw the tracking sheet on this NCA to "clarify" the request. The commenters were unsure of the reason for opening the tracking sheet and the scope of the NCA, e.g., to review all nebulized beta adrenergic agonists, just levalbuterol, or if CMS intends to explore the advantages of levalbuterol over racemic albuterol. The commenters thought that the tracking sheet should be "clarified" and an additional comment period allowed. Given our proposed decision that no national coverage determination is appropriate, it is not necessary or appropriate to make this change at this time.

Twelve commenters asked about the affect of this NCA on the local Medicare contractor's policy that had been published in draft.

A commenter also questioned whether the NCA process can endorse or establish claims for drug products that have not been approved by FDA, or actually prohibited by FDA. CMS does not endorse or make marketing claims for products or drugs. CMS has authority under the Social Security Act to make payment for certain off-label uses of drugs and biologicals under Part B when it determines that such uses are reasonable and necessary for the diagnosis and treatment of an illness or injury.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member," as stated in § 1862(a)(1)(A). This analysis has no effect on drug coverage under the prescription drug benefit program created by Part D.

CMS focused its analysis on the following questions.

Questions:

1.

Is the evidence sufficient to conclude that nebulized beta agonist therapy improves health outcomes when used in the home by Medicare beneficiaries who have lung disease?

2.

If the answer to Question 1 is affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predict a favorable health outcome?

Question 1

Current evidence-based clinical guidelines note the use of beta-adrenergic agonist bronchodilator medications as an important part of the therapeutic regimen for patients with chronic lung disease marked by airflow limitation or obstruction such as asthma and/or COPD.

A review of the scientific literature also demonstrates the beneficial effects of beta-adrenergic agonist bronchodilator drugs in the treatment of asthma and COPD both in the acute disease state and for chronic disease management. The studies reviewed addressed disease control measures (exacerbation rates, symptom control, hospitalization rates, subjective breathlessness, etc.), changes in pulmonary function as measured by FEV1 and FVC, medication side effect profiles and adverse events. The evidence demonstrates that beta-adrenergic agonist bronchodilator therapy can improve disease control and pulmonary function measures when compared to placebo. Though the evidence was derived largely from facility-based outpatient experience, we believe that these results are generalizable to the home for most Medicare beneficiaries, given the relative simplicity of nebulizer use.

In conclusion, we find that the home use of nebulized beta-adrenergic agonist drugs (alone or in combination) for the treatment of chronic lung diseases marked by a reversible component of bronchospasm can be beneficial as part of overall disease management strategy. Thus we propose that the Question 1 be answered affirmatively.

Question 2

The answer to Question 2 is complex. As noted above, current evidence-based clinical guidelines discuss the use of beta-adrenergic agonist drugs in the treatment of asthma and COPD both in the acute disease state and for chronic disease management. By and large, these drugs are not used as sole therapy in chronic lung disease. Rather, they are included in stepwise treatment models that often include other classes of drugs such as corticosteroids, anticholinergics, anti-inflammatories, and methylxanthines. Other approaches including therapy for comorbid conditions, lifestyle modification, limited exposure to allergens and irritants, or surgery may also be recommended in guidelines. The myriad factors involved in the treatment make it difficult to establish a national policy with respect to “particular items” under Title XVIII.

By and large, the published guidelines have made recommendations for classes or subclasses of drugs rather than for specific drugs based on disease severity and treatment goals such as chronic disease management versus acute symptom control. These guidelines do not address the therapeutic effect of one beta-adrenergic agonist drug versus another. In general, guidelines that discuss the delivery of these drugs recommend that administration via a MDI with a spacer be tried first. There is considerable evidence that MDI use achieves therapeutic results that are comparable to those achieved by the use of nebulizers. Dolovich et al. (2005) published a systematic review of the effect of the type of administration device on the efficacy and adverse events of inhaled therapies. They include a detailed discussion of the advantages and disadvantages of the various devices.

Short Acting Beta Agonists Administered Alone

There is a large body of good evidence derived from clinical studies of the various members of this class that short acting beta adrenergic agonist therapy, whether administered via MDI or nebulization, successfully reverses acute and chronic bronchospasm, including bronchospasm caused by asthma and COPD. There is debate about the relative tolerability of the various marketed preparations, which we address below.

Racemic Albuterol and Single Enantiomer (Levalbuterol, marketed as Xopenex®)

The theoretical contention, derived from animal studies and *in vitro* pharmacologic investigations, for claims of clinical superiority for levalbuterol over racemic albuterol is interesting. However, the evidence reviewed is not adequate to conclude that the use of one marketed short acting beta-2 selective adrenergic agonist over another (e.g. albuterol versus levalbuterol) provides any consistently predictable clinically meaningful benefit in the treatment of lung disease. The evidence reviewed notes similar results and adverse event profiles in both the emergency department and other outpatient settings when the drugs are compared. We note that the label for levalbuterol includes warnings similar to other drugs in this class. An excerpt is presented below.

WARNINGS:

1. Paradoxical Bronchospasm: Like other inhaled beta-adrenergic agonists, Xopenex Inhalation Solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Xopenex Inhalation Solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

2. Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Xopenex Inhalation Solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

3. Use of Anti-Inflammatory Agents: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients.

Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

4. Cardiovascular Effects: Xopenex Inhalation Solution, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Xopenex Inhalation Solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Xopenex Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

We do note that in many of the trials that used multiple beta adrenergic agonists, the study design was based on a comparison of the active treatment (either drug) versus placebo, rather than on a comparison between active treatment arms (drug A versus drug B.) Thus the post hoc attempts to find significant differences between drugs were often methodologically difficult to support. Furthermore, we found that examination of data in the text and tables of various published articles served to provide significant information supporting therapeutic equivalence rather than true therapeutic difference.

The studies reviewed are generally characterized by small sample sizes and short duration of study length. Studies were conducted in both the emergency department and other outpatient settings, although the majority accessed treatment in the acute care setting. In addition, a limited number of studies specifically address the use of nebulized medications. Therefore, generalizability of treatment effect for persons with chronic stable disease is limited. More studies are needed that evaluate patient drug usage in the outpatient setting with chronic stable disease states over a much longer period of time.

While a few preclinical studies have examined the potential for S-albuterol to counteract bronchodilation and promote inflammation in animal studies, no clinical studies have provided adequate data that the chemical composition of levalbuterol has a beneficial advantage by decreasing inflammation of the bronchial tree or otherwise minimizing adverse events associated with the administration of the albuterol.

We have not reviewed any evidence that would lead us to conclude that levalbuterol produces worse outcomes than racemic albuterol. Since racemic albuterol is half levalbuterol we would be surprised if such evidence was brought to light.

In Table 1 of the FDA label for Xopenex Inhalation Solution (levalbuterol) the pharmacokinetic data are presented comparing the two preparations. Specifically, the area under the curve (AUC) for R- albuterol was 2-fold higher following the single nebulized administration of 1.25 mg levalbuterol versus 2.5 mg of racemic albuterol. However, this difference was not apparent after cumulative dosing every 30 minutes with either 4 total doses of levalbuterol or racemic albuterol. (Accessed January 3, 2007 at http://www.fda.gov/cder/foi/nda/2003/020837_S010_Xopenex_APPROVAL%20PACKAGE.pdf)

When a patient with asthma or COPD experiences an exacerbation (temporary worsening) of symptoms, it is not unusual for that patient to receive several nebulizer treatments over the course of an hour or two. Thus, the cumulative lack of difference in AUC may be more predictive of actual clinical experience than the single dose AUC.

The current record does not provide sufficient evidence of a clinically meaningful difference that can be reliably predicted in the treatment of an individual beneficiary with a single enantiomer compared to a racemic preparation of a nebulized short acting beta adrenergic agonist. We are aware that some beneficiaries may express an individual preference for one or another preparation based on personal experience, and we believe that the clinical significance of this is best determined by the local Medicare contractors.

Long Acting Beta Adrenergic agonists (LABAs)

We are aware of reports linking the use of LABAs with an increased risk of death in patients with asthma. The label for arformoterol, the only LABA currently marketed in the U.S. for nebulized administration, includes the black box warning and the following indication: "...maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema." Clinical evidence and various guidelines provide recommendations for the specific use of these medications based on disease stage and severity.

Studies evaluating the use of LABAs alone or in combination as a treatment option note similar results with improvement in FEV1 for patient with asthma or COPD as already described. These studies also compared patients at varying stages of disease and in general utilized the MDI method of medication delivery. Therefore, current clinical guidelines and patient symptoms play an important part in determining the appropriate use of these medications. The myriad factors involved, however, make it extremely difficult to define a precise patient population that is necessary for a national coverage determination.

We note that individual LABAs are indicated for the maintenance treatment of beneficiaries with asthma and/or COPD requiring maintenance bronchodilator therapy that is not adequately accomplished by short acting beta-adrenergic agonist treatment. The FDA approved labels for arformoterol (Brovana) and salmeterol (Serevent) note that LABAs are not appropriate to treat acute symptoms.

BROVANA is not indicated to relieve acute respiratory symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta2-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen,

SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled, short-acting beta2-agonist for this purpose as well as warn them that increasing inhaled beta2-agonist use is a signal of deteriorating asthma.

Local Medicare contractors are in the best position to make reasonable and necessary determinations for uses of LABAs.

Fixed Combinations including Beta Adrenergic Agonists

One nebulized combination therapy is currently available for the management of patients with COPD (ipratropium/albuterol). The evidence reviewed demonstrates improved FEV1 measures when comparing the combination to the use of either component taken singly. However, we are unaware of evidence of significant differences in clinical outcomes when comparing marketed combinations for nebulized administration versus sequential or concurrent administration of both active drugs. We are not aware of any claims that the mixing of ipratropium and albuterol creates a new molecular entity; indeed we have been told by stakeholders that the two drugs exert their effects as single agents.

We note for completeness that two fixed combination preparations of budesonide and formoterol are marketed for metered dose inhalation. These are not currently marketed for nebulized administration.

The trials compared patients at various stages of their disease as classified by baseline FEV1. Therefore, it is difficult to determine or conclude which specific subset of patients would most benefit from this therapy, other than the general conclusion previously stated that combination therapy compared to single therapy with one drug has been shown to improve FEV1 for patients with COPD. No nebulized combination therapies are currently FDA approved final products for use in asthmatic patients.

Summary Answer for Question 2

It is crucial to establish that the beneficiary in fact has a condition for which this therapy is indicated. A variety of other acute and chronic conditions beyond the scope of this review may cause symptoms or signs of bronchospasm (wheezing, dyspnea or hypoxemia), for example heart failure, aspirated foreign bodies, and tumors.

Comprehensive approaches are often necessary to treat the conditions for which nebulized beta adrenergic agonist therapy is indicated.

Though it is a relatively straightforward task, the safe and correct preparation and use of a nebulizer and the associated drug requires the beneficiary or his caregiver to demonstrate a basic level of cognitive ability and dexterity.

Though we focused our review of these drugs on their uses in asthma and COPD we are aware of the many possible clinical presentations and therapeutic interventions that are possible. Our local contractors, who may review the beneficiary's medical record, are better positioned to determine if the use of a particular nebulized beta adrenergic agonist is reasonable and necessary.

IX. Conclusion

On December 20, 2006, we initiated the NCD process by opening a tracking sheet for Nebulized Beta Adrenergic Agonist Therapy for Lung Diseases (CAG-00354N). After examining the available medical evidence, we propose that no national coverage determination is appropriate at this time, and that the §1862(a)(1)(A) decision should be made by local contractors through a local coverage determination process or case-by-case adjudication. See *Heckler v. Ringer*, 466 U.S. 602, 617 (1984) (Recognizing that the Secretary has discretion to either establish a generally applicable rule or to allow individual adjudication.) See also, 68 Fed. Reg. 63692, 63693 (November 7, 2003).

Our examination of the published medical evidence does not provide sufficient information that would enable CMS to define specific populations of patients who would benefit from a particular treatment with particular medications at this time. Because a national coverage determination is defined, in part, as including "whether or not a particular item or service is covered nationally" under title XVIII, §§ 1862(l), 1869(f)(1)(B), we do not believe a national policy is possible or prudent at this time. Still, in order to maintain an open and transparent process, we are seeking comments on our proposal that no national coverage determination is appropriate at this time. We will respond to public comments in a final decision memorandum, consistent with the spirit of §1862(l)(3).

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